THE REGULATION OF RESPIRATION AND CIRCULATION DURING THE INITIAL STAGES OF MUSCULAR WORK.

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In the present paper we propose to describe the changes in ventilation, blood flow, pulse rate, respiratory exchange and alveolar CO_2 tension taking place in man during the first few minutes of light or heavy work and we shall attempt further an inquiry into the mechanism of these changes. The experiments have been made by means of the bicycle ergometer and respiration apparatus described in another paper[1] in which also the main parts of the technique employed have been set forth in detail.

We have made experiments on six different subjects. Three of these, J. L., F. N. and J. J., are trained, more or less, to sudden and violent exertions, while the other three, though able to do a fair amount of work over a long period, are not trained to sudden exertions. When told to start with a heavy load the three first named subjects will begin at a very rapid rate, which soon declines, while the other three—even when told to start as rapidly as possible, and meaning to do so—will begin comparatively slowly and work up during a certain time. (Compare for example Exps. X and IX, p. 135.)

On the subjects J. J., J. K. and H. P. we have made determinations of pulmonary volumes, ventilations and rates of work only, under varying conditions. On A. K. and F. N. we have made a few "complete" experiments involving determinations of the respiratory exchange and the composition of the alveolar air at several moments, especially during the first minute of work. The most detailed study has been made on J. L. The respiration of this subject is deep, slow and extremely regular, which greatly facilitates the correct sampling of the alveolar air. We wish to state explicitly—though it may seem superfluous—that the breathing in all cases (except when a subject was told to breathe

[1] *Skand. Arch. Physiol.* xxx.

forcibly) was quite involuntary. The subjects J. J., J. K. and H. P. had no idea whatever of the character of their breathing or of the changes which we expected on beginning work. In our own cases the changes observed, when we made our first experiments in the early spring of 1911, were so startling and so contrary to our expectations that we were led to undertake the present special study. During the two years which have since elapsed we have made a large number of experiments of which selected cases only are directly referred to in the following.

We shall begin by describing for each physiological function separately the changes which take place at or just after the transition from a state of comparative rest—sitting on a bicycle with the feet on supports—to muscular work varying between 300 and 2200 kilogram meters (kg. m.) per minute.

1. *The mean capacity of the lungs.* The mean capacity of the lungs during respiration has been defined by Bohr[1] as the average between the volumes present at the end of inspiration and expiration respectively. Bohr found that the mean capacity was increased during muscular work, and he expressed the opinion that this constitutes an important regulatory mechanism by which the alveolar surface is increased and the resistance against the passage of blood through the lungs diminished. We are unable to agree with Bohr's conclusions. We have observed cases (J. L., A. K.) where no increase whatever in mean capacity takes place even during heavy work and others showing probably[2] a comparatively slight increase. In one case only (J. K.) have we seen a sudden and considerable increase (0·7 l.) take place just at the beginning of work. We believe from what we have seen that the biological importance of variations in mean capacity is very slight, but we propose to put off the discussion until more material shall have accumulated.

2. *The ventilation of the lungs.* We find in all the cases examined an abrupt rise in ventilation when work varying from 300 to 2200 kg. m. per minute is suddenly started. The immediate increase is on the whole greater with heavier work but there are large individual differences, depending, we believe, chiefly on training to sudden exertions. In the subjects J. L., F. N. and J. J., who are thus trained,

[1] *Deutsches Arch. f. klin. Med.* LXXXVIII. p. 385. 1907.

[2] That is, if we assume with Bohr (*l. c.* p. 411) that the total capacity (vital capacity + residual air) is a constant. This assumption holds true approximately in the case of J. L. so long as the body position is not altered, but has not so far been tested in any other case.

the immediate increase in ventilation is very great with heavy work. In A. K., J. K. and H. P. who are not trained to sudden exertions the abrupt increase is not so pronounced though always present.

J. L., F. N. and J. K. practically always begin work with a deep and rapid inspiration (Fig. 1) coinciding absolutely with the beginning of

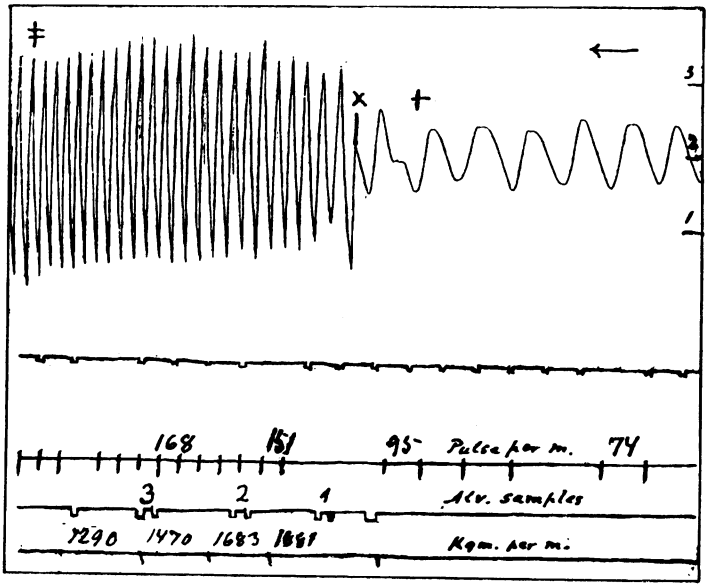

Fig. 1. J. L. Transition from rest to work. Exp. X. Scale in liters. Time in $\frac{1}{10}$ minutes. + Ready, × Begin, ‡ Stop.

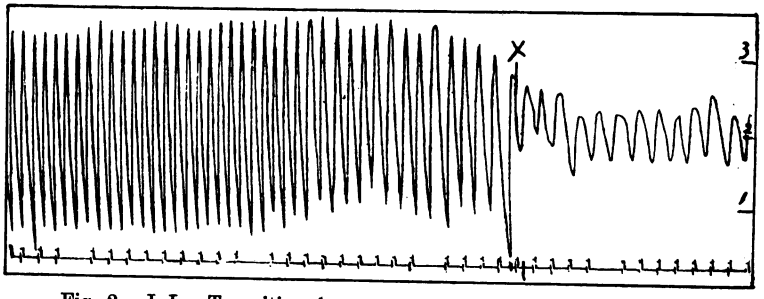

Fig. 2. J. L. Transition from rest to work of about 800 kg. m.

work, but we have seen in a few cases, when the word to begin was given while an expiration was in progress that this may be finished at a normal or slightly increased rate and depth, before the deep and rapid inspiration takes place (Fig. 2).

The full line curves in Fig. 3 represent graphically the observed total[1] ventilations calculated per minute (frequency × depth of breath, measured moist at 37°) for work varied between 350 and 1880 kg. m. per minute. These curves are typical also for F. N. and J. J. It is a very significant fact that with heavy work the rate of the second and third breath is slower than the first, while the depth may be diminished also. A decrease in ventilation is thereby produced, but 10 to 15 seconds after the beginning of work the ventilation is again increased and a maximum is generally reached in two to four minutes.

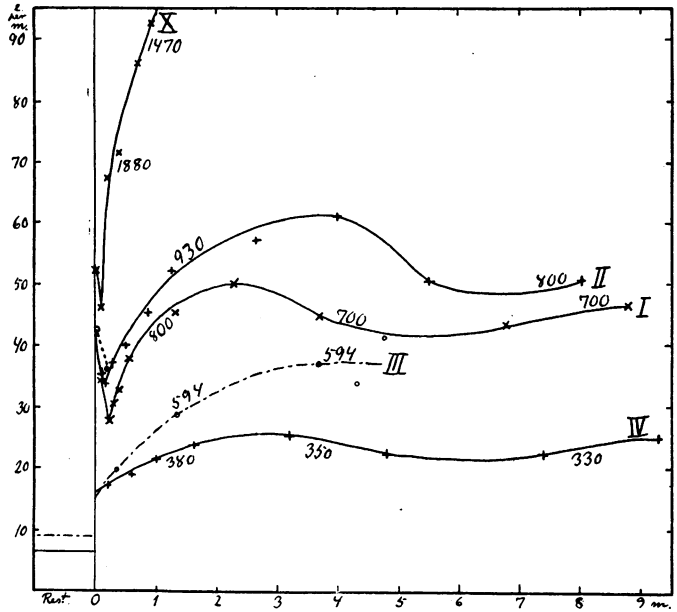

Fig. 3. Ventilation curves. At *O* beginning of work. Figures along curves kg. m. per minute.

This maximum is followed by a second gradual fall down to a more or less constant level depending upon the rate at which work is being performed. With light work (300–400 kg. m.) the fall in ventilation after the first breath is not a constant feature and we have selected a record which does not show it.

In one experiment the subject J. L. was told to work at a rapid rate and with a heavy load (3 kg.) but at the signal to begin current was not turned on to the magnets of the ergometer. The resulting respiration

[1] Figures relating to the alveolar ventilation are given in the protocols, pp. 133–136.

during the first few seconds was practically the same as if there had been a heavy load, though the actual work performed was insignificant. (Fig. 4 and short dotted line o----o on Fig. 3.)

The curve ——— on Fig. 3 gives the ventilation of A. K. in Exp. III (Fig. 5) which shows the smallest initial rise so far measured. This curve is roughly typical also for J. K. and H. P. The abrupt rise

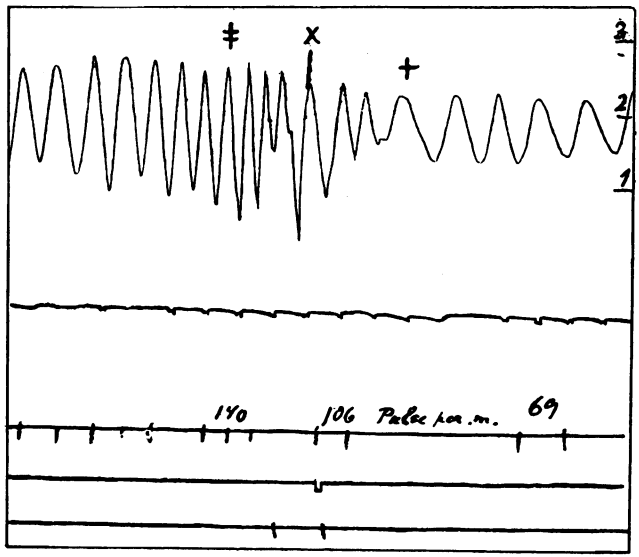

Fig. 4. J. L. Transition from rest to work without any load on the machine.

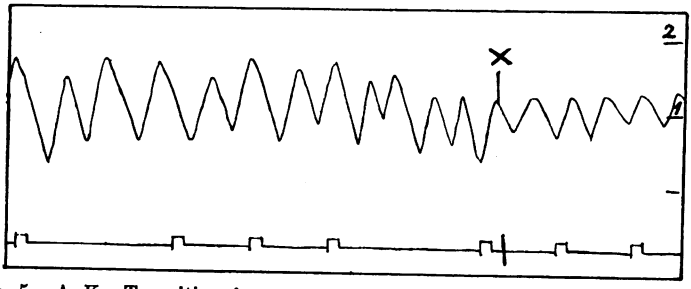

Fig. 5. A. K. Transition from rest to work of about 600 kg. m. Exp. III.

may be of very variable magnitude but is never of the magnitude observed in the other group. The decrease in ventilation after the first breath is observed only occasionally and the rule is a gradual increase up to a comparatively constant level.

We have made no special study of the influence of work upon respiration rate or depth taken each by itself, because that would

probably require a very large material to give results of any value. Some data bearing upon these points are found in the protocols.

3. *The pulse rate.* We have never been able to count the pulse during the first seconds of bicycling on the ergometer, but it is known from the investigations of Miss Buchanan[1] that the pulse rate is increased from the first beat occurring after the beginning of work. Miss Buchanan has shown us the very great kindness to take some electrocardiograms on subjects starting work on a stationary tricycle. The work could not be measured but in some cases at least it appears from the symptoms to have been rather heavy. Miss Buchanan has sent us the following table of experiments:

Pulse rates per minute.

	Resting	½ sec.	2 secs.	10 secs.	20 secs.	1—2 m.	5—7 m. after hearing signal to begin work	
R. W. D.	42	74	84	90	105	120	120–127	Not heated by 5 mins. exercise. Great footballer.
W. B.	55	67	80	96	100	100	115	Not much heated.
W. Ch.	58	78	85–90	100	100	140	150	A good deal heated.
C. G. D.	60	72	75	84	88	96–108	100	Not at all heated.
G. H. B.	64	72	80	90	90	100	100–103	Not at all heated.
R. P. H.	68	100	106	120	124	135–140	135–140	Felt warm.
F.B.S.H.	72	90	96	105	108	110	120	Not heated.
Dr H.	72	(Heart effects absorbed by those of hand muscles)				180	—	Worked very vigorously. Much heated and quite out of breath at the end of two mins.

From the experiments on R. W. D., C. G. D. and R. P. H. we have constructed the typical curves Fig. 6. It is evident that there is in all cases an abrupt rise in the pulse rate on starting work. The rise is followed by a further increase which is very rapid at first. The maximum is practically attained within one or two minutes. From our own experiments we have included a fragmentary curve showing the pulse rate of the subject F. N. while doing the very heavy work of 2200 kg. m.[2].

4. *The absorption of oxygen.* The methods employed for determinations of respiratory exchange in periods comprising a few or even one single respiration are described in the paper quoted above. We have generally taken a determination about 12 seconds after the start

[1] *Oxford Jun. Scientific Club.* 1909.

[2] In our experiments the subject puts his feet on to the pedals on the word "Ready." This is often accompanied by somewhat irregular breathing and by an increase in pulse rate. See Fig. 1.

and then two more during the first minute (see signals in Fig. 1). The later determinations and also the determinations made during rest comprise a large number of respirations and are certainly more accurate. In order to obtain information about the oxygen absorption during the first few seconds of work we have made some special experiments, similar in technique to our circulation rate measurements[1]. The subject (J. L.) was sitting on the bicycle with his feet on the pedals ready to start. He breathed through a mouthpiece and a three-way tap. After an ordinary inspiration the tap was turned and the expiration made into the recording spirometer. An alveolar sample was taken into a vacuous vessel from this expiration and while the tap was closed the subject started at a rapid rate. After three to four seconds the subject expired again into the spirometer, this time down to the residual air, and a second alveolar sample was taken. From the record we could determine the volume of air enclosed and the duration of the experiment, and the analysis of the two samples of alveolar air showed the decrease in oxygen percentage from which the absorption of oxygen per minute could be calculated.

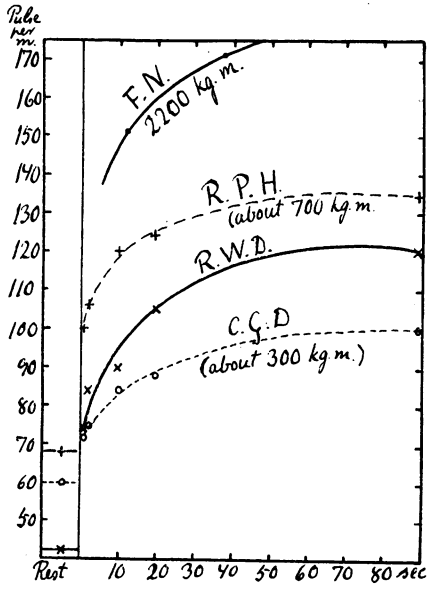

Fig. 6. Pulse rates per minute during transition from rest to work.

In control experiments of this kind made during rest we found normal O_2 absorptions of about 300 c.c. per minute and in three work experiments of 2·8, 4·6 and 4·5 seconds duration we found 200, 250 and 750 c.c. respectively. It is evident from these results, when they are compared with the values found after 12 seconds and later, that the increase in oxygen absorption is not abrupt but takes place gradually though often very rapidly and there would seem even to be a latent period of a couple of seconds.

A graphic representation of the changes in oxygen absorption taking place during the first minutes of work is given in Fig. 7. After about

[1] *Skand. Arch. Physiol.* XXVII. 1912.

12 seconds the absorption has risen from the resting value of about 250 c.c. per minute to something between 750 and 1500 c.c. and thereafter a further increase takes place until an absorption corresponding to the work (or in most cases rather in excess of it) has been reached.

5. *The circulation rate.* From the observed changes in oxygen absorption it is legitimate to infer that corresponding changes take place in the circulation rate. During the first 6–10 seconds at least the venous blood reaching the lungs must have practically the same oxygen percentage as during rest and as the arterial blood is always practically saturated with oxygen the increase in O_2 absorption can be due only to

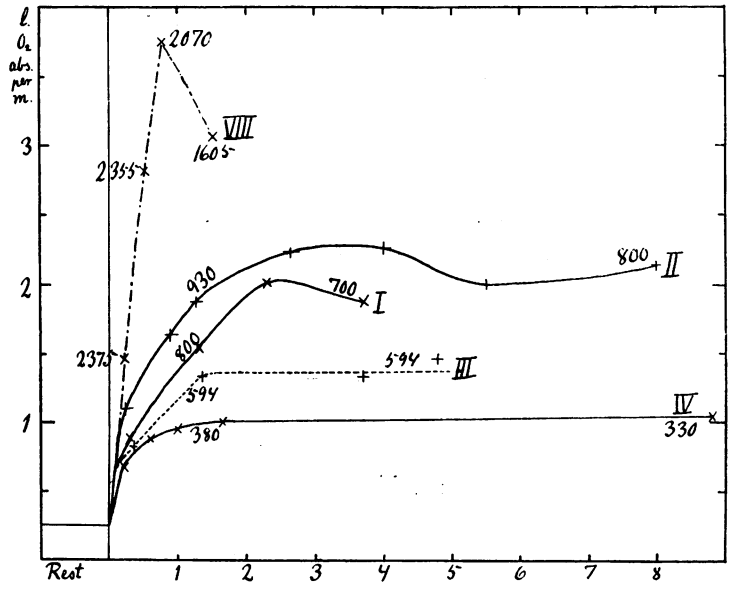

Fig. 7. Curves showing oxygen absorption before and during work. Figures along curves kg. m. per min.

an increase in circulation rate and must be very nearly proportional to that increase. Later on the relations between O_2 absorption and blood flow become more complicated because the oxygen percentage of the venous blood may be and often is diminished[1]. Even then however a considerable increase in O_2 absorption is explicable only by a corresponding, though often smaller, increase in the circulation rate.

[1] Krogh and Lindhard, *Skand. Arch. Physiol.* XXVII. 1912. The further possibility of oxydations taking place in the lungs themselves may be disregarded according to recent investigations by Evans and Starling (This *Journ.* XLVI. p. 413) and by Henriques.

Our results indicate therefore that the blood flow through the lungs begins to rise almost immediately after the beginning of work though there may be a latent period of a couple of seconds. A very rapid rise takes place at first and after 12 to 15 seconds when the pulse rate is perhaps doubled the circulation rate is at least tripled and perhaps more than quadrupled.

The systolic output of the heart is probably often diminished during the first two or three beats because the rate is increased while the venous supply is still inadequate, but thereafter it rises rapidly and after a very short time we get what has been termed by one of us[1] an adequate supply by which the systolic output attains its maximum and the blood flow per minute becomes proportional to the rate of beat.

For direct determinations of the circulation rate during work we must refer to the paper quoted above and we shall give here only a couple of measurements of the rate during the first 6 to 8 seconds of very heavy work which was begun just after the expiration for the first alveolar sample.

		Blood flow per minute	O_2 absorbed per liter blood
J. L.	Resting	4·0 liters	65 c.c.
	Working, 8·4 secs.	13·1	83
F. N.	Resting	3·2	81
	Working, 6·0 secs.	21·1	75

6. *The alveolar CO_2 tension.* On the changes in alveolar CO_2 tension taking place during work it is possible to speak with great reservation only. The difficulties in the way of obtaining even approximately correct values for the average CO_2 tension have been pointed out in another paper[2]. We became aware of these difficulties very gradually while the work was in progress. Our earlier material is therefore of little value in this respect and even from the results of our latest experiments we cannot compute quite reliable figures.

In the later experiments we have taken samples denoted *b*-samples of alveolar air from the last portion of the natural expiration, when this was deep enough. We find that in the first stages of heavy work (about 12 seconds after beginning) there is invariably a considerable fall below the resting value in the CO_2 percentage of such samples[3]. When the respiration increases considerably in depth the variations in alveolar CO_2 tension which take place in the course of every single breath must

[1] *Skand. Arch. Physiol.* XXVII. p. 126. 1912.

[2] *Skand. Arch. Physiol.* XXX.

[3] With light work the fall in alveolar CO_2 is not constantly observed but it is probably present nevertheless during the first one or two respirations.

become greater. We must conclude therefore that there is a fall also in the average alveolar CO_2 tension and it seems probable that this fall is even greater than that observed in the *b*-samples. How great it is we do not know. In our own opinion our figures, which are given in the protocols at the end of the paper, have a qualitative significance only and the results which they can yield can be summarised as follows:— When the first sample is taken about 12 seconds after the beginning of heavy work the average alveolar CO_2 tension is distinctly lower than during rest (perhaps about 1 % or 7 mm.). When the next sample is taken, 12 to 18 seconds later, the CO_2 tension is rising again. In some cases it is still distinctly below the resting value but in others it is perhaps higher. Later on the *b*-samples show CO_2 percentages which are on the whole higher than during rest. The calculated CO_2 percentages of the alveolar expired air are also generally higher than during rest and we believe therefore that the average CO_2 tension is increased, but we do not venture to affirm positively that this is the case, and the increase in CO_2 tension cannot be considerable even when the ventilation is increased tenfold[1]. We have planned a special investigation of this very important problem as the next point on our programme.

7. *The respiratory quotient* as determined from the CO_2 percentage and the O_2 deficit of the alveolar expired air rises almost invariably when muscular work is begun. With heavy work the quotient of the first sample (after about 12 seconds) is often above unity and a further increase may take place. A rise in quotient during the initial stages of work does not mean of course that a change in metabolism has taken place since the venous blood passing through the lungs is still unchanged. It means only that the balance between ventilation and blood flow[2] has been altered, that the former has been increased out of proportion to the latter. That this is so in most cases during the first seconds of work is evident enough from the ventilation curves and the O_2 absorption curves given above (see also Fig. 13) and the respiratory quotients found only

[1] Hough (*Amer. Journ. of Physiol.* xxx. p. 18. 1912) who has taken Haldane-Priestley samples of alveolar air 10–20 seconds after work, found a distinct increase in CO_2 after light work and a decrease after heavy work. Hough lays special stress on the difficulties in obtaining correct values for the alveolar CO_2 under the influence of work and says that if the expiration by which a sample is obtained is in the least prolonged the percentage is certain to become too high. He believes that he has avoided this error and he has undoubtedly diminished its influence to a certain extent. According to our experience the changes taking place in 10–20 seconds after work are too considerable to allow conclusions to be drawn from his results with regard to the alveolar tensions *during* the work.

[2] Krogh. *Skand. Arch. Physiol.* xxiii. p. 267. 1910.

serve to bear this out. In Exp. III on A. K. (Work 600 kg. m.) and IV on J. L. (Work 350 kg. m.) we have a comparatively slight increase in ventilation at first and normal quotients. That means that when the first sample was taken the increase in blood flow had caught up with the increase in ventilation and the further increases in both have taken place at about the same rate.

The mechanisms by which the observed changes are produced.

It is obvious that changes which take place abruptly at the beginning of work or with a latent period—if any—of less than one second cannot be brought about by any chemical regulation as a result of the processes in the working muscles. If the excess of CO_2 produced in the muscles were responsible for the rise in ventilation there must be a latent period until the blood from the muscles could reach the respiration centre and if, as has been supposed[1], the rise in temperature of the blood during work was the cause of the increased pulse rate it must last a considerable time before this increase could take place. The mechanism which shall produce the abrupt changes must be a nervous mechanism, and so far as the pulse rate is concerned the case has been aptly put by Johansson[2] who concluded from his experiments on rabbits that the motor impulses to the muscles irradiate to the centres governing the heart. We must conclude also that the motor impulses irradiate to the centres governing the respiration.

Johansson expresses the opinion that the increase in pulse rate cannot be due to a reflex innervation from the muscles because it is induced only by voluntary movements on the part of the animal but neither by mere passive movements nor by electrical stimulation. In the case of the heart our material does not lend itself to any more detailed study of the mechanism by which the acceleration is brought about[3] and we can only express our concurrence in Johansson's view.

With regard to the ventilation we think also that the evidence is in favour of an irradiation of impulses from the motor cortex rather than

[1] Mansfeld. *Pflüger's Arch.* CXXXIV. pp. 598–626. 1910.

[2] *Skand. Arch. Physiol.* V. p. 20. 1893.

[3] Such a study has moreover been carried out already by Aulo (*Skand. Arch. Physiol.* XXV. p. 347. 1911). Aulo finds, like Miss Buchanan, that the first and chief effect of muscular work on the heart is a shortening of the diastolic period, while the systole is not affected at all or increased until several seconds have elapsed. Since Hunt has found (*Amer. Journ. Physiol.* II. p. 436. 1899) that exclusion of the vagi has a like effect which sets in immediately, while excitation of the Nn. accelerantes causes shortening of both systole and diastole after a comparatively long latent period, Aulo concludes that the main factor of the increase in frequency is a diminution of the vagus tone.

a reflex from the muscles and this view is supported especially by the fact that a deep and frequent respiration can be induced without any load on the ergometer, when the subject is led to expect that the work will be heavy.

The assumed irradiation of impulses might as far as we can see influence the respiration in three different ways, namely:

1. Through the cortex centres of the respiratory muscles producing respiratory movements independently of and superseding the normal action of the respiratory centre—as in voluntary forced breathing.

2. Through the automatic respiratory centre by impulses adding themselves to the normal impulses emanating from that centre.

3. Through the automatic respiratory centre by causing a sudden increase in the excitability of that centre towards its normal stimulus.

We have attempted to find out, partly by reasoning from the data given above and partly by experiments specially devised for that purpose, which of these possibilities is the most probable.

The first possibility is realised, as mentioned above, during voluntary forced breathing by which a completely uniform (see Fig. 10) and greatly increased ventilation can be maintained, independently (for a certain time at least) of the decrease and disappearance of the chemical stimulus. In pain hyperpnœa[1] we have perhaps an analogous but involuntary innervation. The mechanism of pain hyperpnœa has scarcely been sufficiently investigated to make it certain that it is quite independent of the normal stimulus of the respiratory centre, but it may at all events be carried on after the disappearance of that stimulus.

During work and especially at first the attention of the subject is absorbed by the work and the breathing is quite involuntary. Nevertheless we might have a direct innervation of the respiratory muscles, and the two facts that the initial ventilation corresponds more or less closely to the amount of work expected, and that it comes off whether the expectation is substantially realised or not might perhaps be taken to support this view. We have put the view, which we ourselves were inclined to entertain at first, to a crucial test by experiments in which we varied the chemical stimulation of the respiratory centre

a. by adding CO_2 to the inspired air and

b. by removing CO_2 through forced breathing just before the work.

If the action of the respiratory centre is superseded by direct innervation we should expect these variations to have very little influence or none at all upon the initial breathing during work.

[1] Y. Henderson. *Amer. Journ. of Physiol.* xxv. pp. 310–333, 385–402. 1910.

We found that the addition of about 3 % CO_2 causes a very considerable increase in the initial ventilation above that observed when the same amount of work is performed with atmospheric air (Exp. VII, Fig. 12).

The apnœa produced by one minute's forced breathing during rest is in normal cases continued undisturbed for a certain time after the beginning of heavy muscular work. In one of the experiments on J. L. the alveolar CO_2 percentage (*b*-samples) was brought down by forced breathing to 1·75 %. The apnœa lasted seven seconds after the beginning of work of 1400 kg. m. and the alveolar CO_2 percentage found just after the beginning of respiration was 4·7 %. Before the experiment, during rest, 5·26 % CO_2 was found in a *b*-sample. In a corresponding experiment on J. J. the apnœa lasted for at least ten seconds after the beginning of work. J. J. had no idea whatever that an apnœa would result from forced breathing and did not know whether he respired or not after he had begun to work. In A. K. the alveolar CO_2 percentage was brought down by forced breathing to 2·0. Cheyne-Stokes' breathing (Fig. 9) set in simultaneously with the work, and the CO_2 percentage during the first group of respirations was found to be 3·4 %, but we found that during rest also the apnœa of this subject is interrupted by Cheyne-

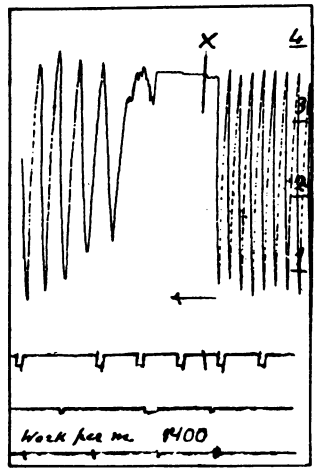

Fig. 8. J. L. Forced breathing. Apnœa continued after the beginning of work.

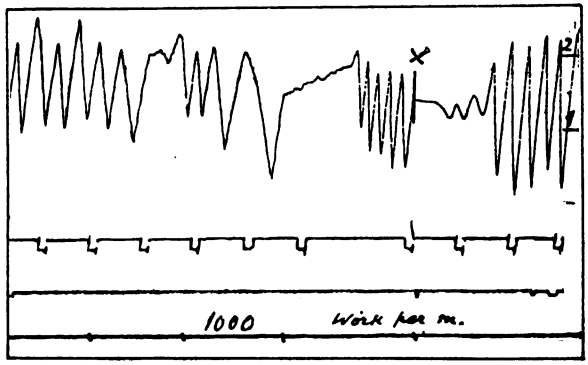

Fig. 9. A. K. Forced breathing of air. Cheyne-Stokes breathing during first stages of work.

Stokes' respiration after a very short interval (Fig. 10)[1]. When the respiration apparatus has been filled with oxygen a normal apnœa is produced by forced breathing and this may be continued for several seconds after the beginning of heavy work (Fig. 11)[2]. When respiration begins during work after forced breathing the ventilation rises with extreme rapidity to a very high rate (Fig. 8, Curve Fig. 12) or begins at once with very deep and rapid breathing (Fig. 11).

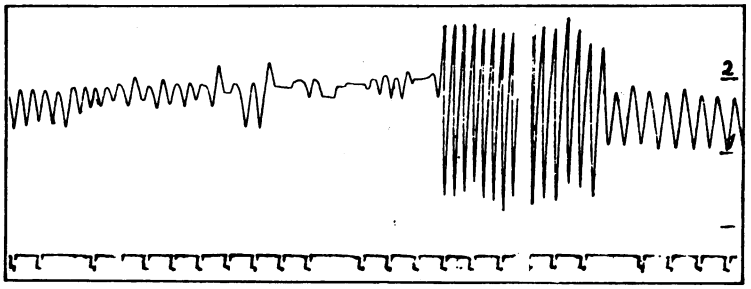

Fig. 10. Forced breathing of air. Cheyne-Stokes breathing during rest.

The results of the CO_2 and apnœa experiments are conclusive in disproving the existence during the initial stages of work of a direct innervation of the respiration muscles superseding the normal action of the respiratory centre.

If the second of the possibilities enumerated above was realised, and the respiration impulses irradiating from the motor cortex at the beginning of work were simply added to the normal impulses, emanating from the respiratory centre, and produced the enormous increase in ventilation by this addition, the effect of an increased alveolar CO_2 tension would be easy to understand, but

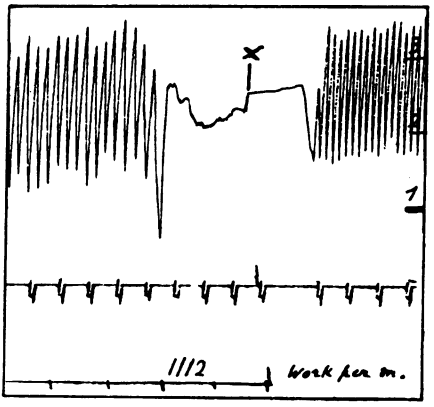

Fig. 11. A. K. Forced breathing of oxygen. Apnœa after beginning work.

[1] This respiration began in the case figured after five seconds. The percentage of oxygen in the lungs must have been ample and the CO_2 percentage extremely low. We hope to undertake later an investigation of the causes producing this type of respiration, and others still more striking, after forced breathing.

[2] All the subjects of the apnœa experiments were much struck with the relief caused by the work after forced breathing and the ease with which it was performed at first.

the apnœa results could not be satisfactorily explained, since they would imply that the impulses from the cortex were not sufficient in themselves to cause any respiration whatever.

We appear therefore to be driven to the conclusion that the mechanism, by which the increased ventilation at the beginning of work is brought about, is a sudden increase in the excitability of the respiratory centre induced by irradiation of impulses from the motor cortex. Such an increase will account, as far as we can see, for all the facts which we have observed. Since, however, the conception of a respiratory centre of variable excitability has been called in doubt[1] it will be necessary before proceeding further to review briefly the evidence concerning this problem.

Lindhard[2] found that under constant conditions an increase in the alveolar CO_2 tension brought about by breathing definite mixtures of CO_2 with air would produce very different increases in ventilation in different people, but for the same subject the increase in ventilation was (normally) a constant and could be taken as an index of the excitability of his respiratory centre.

Lindhard found further that the excitability of a person's respiratory centre could be temporarily altered by definite means: Drugs such as strychnine, morphia and chloral produce effects on the respiratory centre which are completely analogous to their general effects on the nervous system inasmuch as strychnine increases the excitability enormously while morphia and chloral diminish it. Oxygen was found by Lindhard to diminish the excitability of the centre. When the same proportion of CO_2 in 15 %, 21 % and 96 % O_2 was breathed the ventilation was less with 21 % than with 15 % and less again with 96 % O_2.

Haldane and Douglas[3] have been unable to confirm the effects of high (60 %) oxygen percentages and they think that they may be spurious. They contend that the experiments have been of too short duration and that the alveolar samples were perhaps unreliable. The method of taking alveolar samples introduced by Lindhard has however been tested repeatedly[4] and compared with the Haldane-Priestley method but quite apart from this: if with a given percentage of CO_2 in the inspired air the ventilation is less with oxygen than with air the

[1] Douglas, Haldane, Henderson and Schneider. *Phil. Trans. Roy. Soc.* B. CCIII. pp. 185–313. 1913.

[2] This *Journal*, XLII. p. 337. 1911.

[3] *Op. cit.* (*Phil. Trans. Roy. Soc.*), p. 207.

[4] A detailed account of the tests is given in another paper by one of us. *Skand. Arch. Physiol.* XXX.

alveolar CO_2 percentage cannot avoid being higher. That the duration of the experiments was sufficient is evident from the fact that the ventilation remained constant from minute to minute after the first minute or two[1].

Hasselbalch and Lundsgaard[2] have observed the identical effect of oxygen on rabbits in 10 m. experiments after an introductory period varied between 5 and 30 minutes. They have measured both ventilation, alveolar CO_2 percentage and H-ion concentration of the blood and obtained the same result from all sources. Hasselbalch and Lindhard[3] have repeated the oxygen experiments on man during a mountain expedition, using the original technique, and found them confirmed.

We have finally found the oxygen effects confirmed in the case of J. L. (Exp. VI) both during rest and during muscular work in experiments in which the CO_2 percentage was allowed to rise slowly.

The effect of a high oxygen percentage in the air breathed on the respiratory centre must be brought about through an increase in the oxygen percentage of the arterial blood reaching the centre. This increase can at best only be slight, since the arterial blood is normally very nearly saturated with oxygen, and it is to our minds not at all surprising if it should be inconstant and if the oxygen effect cannot be demonstrated on all subjects.

Haldane and Douglas interpret the effects of low oxygen tensions, which they have observed themselves[4], as due to the production of acid substances in the centre under the influence of partial asphyxia. If we assume that such substances are normally present in the centre and may be destroyed when the O_2 tension of the blood rises, their interpretation might perhaps be made to cover the oxygen effects as well. Though acid substances are undoubtedly present in the blood when a subject has been exposed for some time to low oxygen pressures the existence in the respiratory centre itself of substances of an acid nature which are readily oxidizable when the oxygen tension reaches a certain rather high level[5] is purely hypothetical and we believe that the hypothesis ascribing to the oxygen a direct influence on the excitability of the centre offers on the whole the most probable explanation of the various facts observed in connection with oxygen inhalation, but while we are fully convinced

[1] This fact was not explicitly stated in Lindhard's paper.

[2] *Skand. Arch. Physiol.* XXVII. p. 29. 1912. [3] *Ibid.* XXV. p. 361. 1911.

[4] This *Journal*, XXXVIII. p. 401. 1910.

[5] The substance in question cannot be lactic acid, since this acid is oxidizable in tissues (muscles) with a very low O_2 tension, while it is probably not oxidized at all in the blood.

of the reality of the oxygen effect we admit that its correct interpretation is still a matter of legitimate doubt.

Further studies on the excitability of the respiratory centre have been made by Hasselbalch and Lindhard[1] who observed a distinct influence of strong sunlight and chemical light baths in the case of J. L. and others but not on K. H., by Hasselbalch[2] who observed an increased excitability in one case during pregnancy and finally by Hasselbalch[3] who shows that changes in diet, which profoundly alter the alveolar CO_2 tension do so by altering the hydrogen ion concentration of the blood (measured under a constant CO_2 tension) while they have no influence whatever upon the excitability of the respiratory centre, while a substance like morphia has no influence upon the C_H of the blood but increases the alveolar CO_2 tension by diminishing the excitability of the respiratory centre.

The influence of drugs (strychnine, morphia, etc.) upon the respiratory centre is undoubtedly direct and chemical. The influence of oxygen is—at least in our opinion—quite analogous. When chemical light acting on the skin influences the respiratory centre the influence is probably conveyed through sensory nerves and partakes of the character of a reflex. The influence finally which the experiments described in the present paper have led us to assume is purely nervous in character and may probably be analogous to the influence exercised by the brain on reflexes. The respiratory centre is after all a nervous centre and must be subject to nervous influences.

The hypothesis of a sudden increase in excitability of the respiratory centre will explain, as stated above, all the details of our results. In just those cases in which we find a decrease in ventilation after the first breath we find also a decrease in alveolar CO_2 tension[4]. The diminished reaction corresponds to the diminished stimulus, and when the stimulus is again increased the ventilation rises.

When CO_2 in air is breathed the stimulus is increased and with the high excitability the result is an enormous ventilation (Exp. VII, Fig. 12) while the subject feels a most intense craving for air. CO_2 in oxygen produces an effect which is distinctly less pronounced because the

[1] *Skand. Arch. Physiol.* xxv. 1911. Lindhard, *ibid.* xxvi. 1912.

[2] *Ibid.* xxvii. 1912. [3] *Biochem. Ztschr.* xlvi. 1912.

[4] It might be contended perhaps that the time would be too short for these changes in CO_2 tension to make themselves felt in the respiratory centre. The rapid increase in circulation rate will account for this, however, and we may refer moreover to the observation by Haldane and Priestley (This *Journal*, xxxii. p. 258, Fig. 10) of an apnœic pause of three seconds duration immediately after a single deep breath.

oxygen lowers the excitability of the respiratory centre and allows the CO_2 percentage in the lungs to rise much higher (Exp. VI, Fig. 12).

After forced breathing for one minute or more the CO_2 tension fell in our experiments to 2·3–1·5 % and the hydrogen ion concentration of the blood was therefore not only lower than the threshold exciting value but also below the point of neutrality towards the centre ("Apnœpunkt" Hasselbalch) which acccording to Hasselbalch[1] is probably about 10 mm. (1–2 %) CO_2 below the actual alveolar CO_2 tension. When this is so, no amount of increased excitability could induce respirations before the C_H of the blood had exceeded the point of neutrality by just enough to be a minimal stimulus to the very

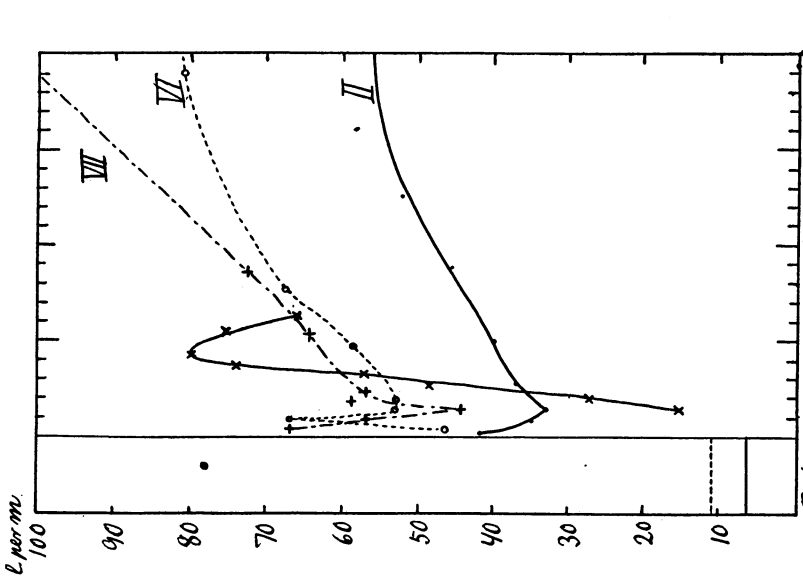

Fig. 12. J. L. Ventilations with nearly equal amounts of work. •——• In air. +—·—+ In air + CO_2. o·····o In oxygen + CO_2. ×——× After forced breathing.

excitable centre, and it is therefore a very important fact that the apnœa lasts on during work until a CO_2 tension has been reached similar to that found in the ordinary work experiments a few seconds after beginning.

Having found that the hypothesis of a sudden increase in the excitability of the respiratory centre is the only one we can find which will agree with all our facts we have finally compared directly the excitability of the centre during rest with that during light work (367 kg. m. per minute). It is generally admitted that during light work there is no lactic acid in the blood and the CO_2 alone is responsible

[1] *Biochem. Ztschr.* XLVI. p. 430, 1912.

for the stimulation of the respiratory centre and for the ventilation. The results are given in detail in the protocol (Exp. XI) and we need only refer to Fig. 13. It will be noticed especially that with the same CO_2 percentage in the *b*-samples of alveolar air (6·45 %) the ventilation during rest is much smaller (8·6 l. per minute) than during the work (26 l. per minute). The average alveolar CO_2 tension is almost certainly lower in the latter case than in the former. The excitability of the centre must therefore have been considerably increased.

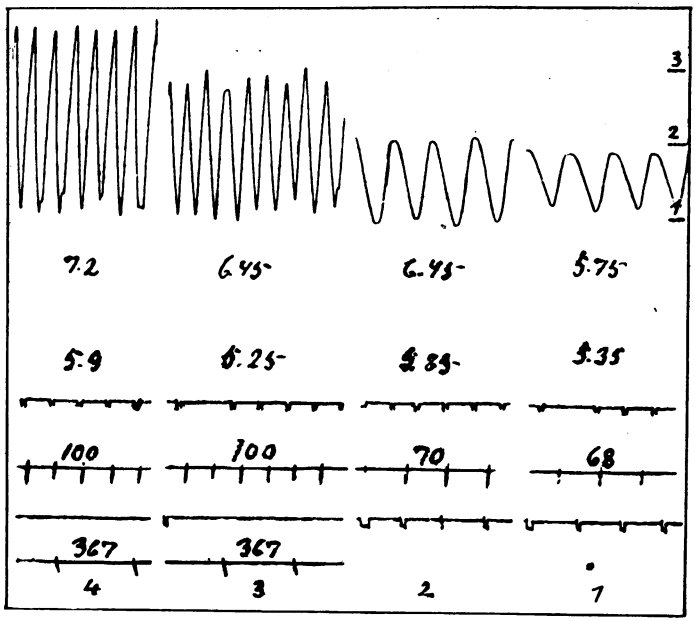

Fig. 13. J. L. 1. Ventilation in air. Rest. 2. Ventilation in air with 3·2 % CO_2. Rest. 3. Ventilation in air. Work. 4. Ventilation in air with 3 % CO_2. Work. Upper line of figures = CO_2 %, *b*-samples. Next line of figures = CO_2 % alv. exp. air.

The mechanism of the increase in blood flow and in oxygen absorption, which depends upon the blood flow, requires only a brief reference.

The increase in blood flow is not abrupt but gradual, and there is, sometimes at least, a latent period of a couple of seconds. The mechanism is probably complex, but the chief factor must be an increase in the venous supply caused (1) by the vasodilatation in the working muscles, (2) by a discharge of blood from the splanchnic reservoir, (3) by the pumping action of the leg muscles upon the blood in the veins of the lower limbs. The acceleration of the heart rate has

not in itself any power to increase the blood flow as long as the supply is inadequate and the same holds good, at least partially, of the increase in the force of contraction and in completeness and rapidity of relaxation which are very probably factors in the final adjustment of the heart to the great strain which is put upon it by heavy muscular work.

It is obvious that the reactions in the circulatory and respiratory systems against sudden and violent exertions constitute in their entirety a regulating mechanism of great importance to the organism. If the circulation and the respiration did not adapt themselves to the instantaneous and enormous rise in muscular metabolism, which is coincident with sudden and violent exertion, before the heart and the respiratory centre were acted upon through the blood by the metabolites produced, then sudden and violent exertions on which the very life of most wild animals depends and which may sometimes be very useful, at least, to civilized man himself, could not possibly be sustained for more than a fraction of a minute. The working muscles would be hopelessly asphyxiated before the fresh supply of oxygen could reach them and the excess of CO_2 be got rid of.

The ideal condition would be of course that the circulation and the respiration were adapted to the changing needs as instantly as the muscles themselves. This ideal is not realised in any of the persons so far examined by us and some of them fall considerably short of it, but even in these the mechanism by which the ideal can be approached can easily be shown to exist.

The amount by which the actual adaptation falls short of the ideal is responsible for the fact that for a certain time, from two to four minutes after the beginning of work in most of our experiments, the heart and respiratory muscles must do work in excess of the average corresponding to the requirements to make up for the time lost during the first minute. We have found that it is extremely difficult to sustain the muscular efforts during this period, and generally the work performed per minute will drop down 10 % or more.

Summary.

At the beginning of heavy work—especially in persons trained to sudden and violent exertions—there is an abrupt rise in pulmonary ventilation and heart rate. The blood flow (as indicated by the oxygen absorption in the lungs) is increased evenly but very rapidly.

After the first breath the ventilation generally falls somewhat during 8–12 seconds and then rises again. During the same time and before there is a considerable fall in alveolar CO_2 tension which is likewise followed by an increase.

The respiratory quotient rises rapidly to or above unity. Fig. 14 is a graphic summary of the changes observed in a typical experiment.

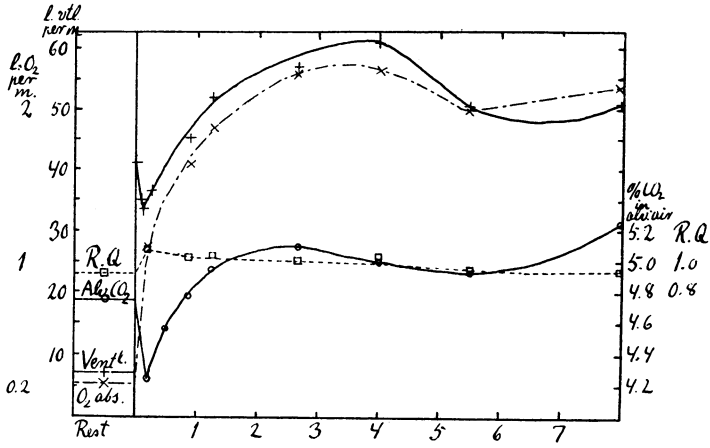

Fig. 14. J. L. Changes in ventilation, O_2 absorption, alveolar CO_2 (*b*-samples) and resp. quotient at the beginning of work of 800 kg. m.

Evidence is brought forward to show that the rise in ventilation like the increase in heart rate is not produced reflexly but by irradiation of impulses from the motor cortex.

In the case of the ventilation these impulses are found to act indirectly through the respiratory centre by suddenly increasing its excitability towards hydrogen ions.

The mechanism disclosed provides a very rapid though not instantaneous adaptation of the respiratory and circulatory systems to sudden muscular exertions. Without it such exertions could not be kept up by the organism for more than a fraction of a minute.

Protocols of Experiments[1].

I. J. L. May 31, 1911, 10.30 a.m. Bar. 767, Temp. 20·7°, Load 2·0 kg.

1 Time from beginning of work, minutes	2 Duration of resp. exp., minutes	3 Frequency of resp. per minute	4 Depth of resp., c.c. (37° saturated)	5 Alveolar ventilation per m. l. (0°, 760 mm.)	6 Alveolar O_2 %, *a* samples	7 Alveolar CO_2 %, *a* samples	8 Alveolar expired air CO_2 %	9 Oxygen absorbed per m. c.c. (0°, 760 mm.)	10 Respiratory quotient	11 Work per minute, kilogram meter	Remarks
−3·0	0·693	7·2	904	4·25	15·42	5·23	4·85	270	0·76	800	Insp. air 0·01 CO_2, 22·21 O_2
+0·3	0·527	11·4	2924	25·85	16·33	5·28	4·88	894	0·90		
										800	
+1·3	0·326	15·3	2965	35·10	16·08	5·04	4·66	1545	1·06		Insp. 0·00, 21·04
+2·3	0·332	18·1	2770	38·40	15·14	5·42	5·02	2015	0·93		
+3·7	0·439	15·9	2810	34·50	14·98	5·86	5·43	1880	0·99	700	
+6·8	0·458	17·4	2490	33·00							
+8·8	0·573	16·6	2800	35·60						700	

II. J. L. June 12, 1911, 11.30 a.m. Bar. 754, Temp. 15·4°, Load 2·5 kg.

1	2	3	4	5	6	7	8	9	10	11	
−2·4	0·606	8·2	798	4·03	15·26	5·11	4·75	210	0·91		
											Insp. 20·99 O_2
+0·21	0·222	13·5	2760	28·10	16·54	4·58	4·24	1100	1·08		
+0·49	0·149	13·4	2985	30·35	—	4·93	4·56	—	—		
+0·87	0·144	13·9	3335	35·40	15·76	5·16	4·78	1635	1·03		
+1·25	0·122	15·5	3365	39·90	15·56	5·34	4·95	1883	1·04	930	
+2·65	0·290	17·2	3320	43·70	15·07	5·50	5·10	2235	1·00		
+4·0	0·289	20·6	2960	46·50	15·18	5·40	5·00	2260	1·03		
+5·5	0·469	17·1	2945	38·05	14·71	5·31	4·92	2000	0·94		
										800	
+8·0	0·320	18·7	2725	38·50	14·07	5·67	5·26	2140	0·95		Insp. 20·14 O_2

III. A. K. June 16, 1911, 11 a.m. Bar. 764, Temp. 15·0°, Load 2·0 kg.

1	2	3	4	5	6	7	8	9	10	11
−5·1	0·507	15·7	582	4·14	15·36	5·18	4·79	251	0·79	
+0·34	0·420	19·0	1040	12·56	14·79	5·50	5·10	823	0·77	
										594
+1·34	0·354	16·9	1703	20·40	14·52	6·34	5·86	1347	0·89	
+3·68	0·362	16·6	2225	27·25	15·93	5·98	5·54	1330	1·13	
										594
+4·78	0·351	19·9	2085	29·00	15·71	6·06	5·61	1468	1·11	

[1] For the experiments made before 12 o'clock the subjects have only had a very light breakfast at 8 or 9. The afternoon experiments were made after a substantial lunch. The differences in alv. CO_2 % found during rest are due to the differences in time of day and also of year.

IV. J. L. June 19, 1911, 11.45 a.m. Bar. 753, Temp. 14·4°, Load 1·0 kg.

1	2	3	4	5	6	7	8	9	10	11	
−2·3	0·549	7·3	873	4·00	14·50	5·37	4·99	236	0·85		Insp. 20·77 O_2
+0·20	0·155	12·9	1340	11·75	14·29	5·55	5·13	684	0·88	360	
+0·60	0·163	12·3	1553	13·30	13·45	5·90	5·45	878	0·83		
+0·99	0·234	12·8	1685	15·35	13·60	5·81	5·38	959	0·85	380	
+1·64	0·312	12·8	1865	17·20	13·98	5·73	5·30	1006	0·91		
+3·17	0·347	14·4	1757	18·00	13·90	5·87	5·43	—	—	350	
+4·79	0·472	12·7	1744	15·80	13·38	6·02	5·57	—	—	325	Insp. 19·69 O_2
+7·43	0·365	13·7	1647	15·90	13·50	5·94	5·49	—	—	330	
+9·33	0·347	14·4	1730	17·75	13·57	5·98	5·53	—	—	330	
+11·5	0·289	13·8	1730	17·05	13·05	6·07	5·62	—	—	330	
+13·7	0·285	14·0	1725	17·20	13·35	5·77	5·34	1045	0·88	330	Insp. 19·94 O_2

V. J. L. June 25, 1912, 2.30 p.m. CO_2 in insp. air. Bar. 760, Temp. 19·0°, Load 2·0 kg.

1	2	3	4	5	6*	7*	8	9	10	11	
−3·5	0·593	8·4	1560	9·29	17·67	6·13	5·68	270	0·58		Insp. 3·95 CO_2 20·70 O_2
−2·5	0·544	9·2	1600	10·45	17·55	6·32	5·86	314	0·62		
+0·16	0·053	18·9	3300	47·95	17·84	6·23	5·54	1356	0·71	1100	
+0·36	0·047	21·3	3450	56·6	17·73	6·42	5·71	1660	0·75		Insp. 3·50
+0·7	0·088	22·7	3440	60·3	17·26	7·10	6·31	1970	0·86	962	21·07
+1·7	0·294	34·0	3150	82·3	17·95	6·25	5·56	—	—	773	
+2·6	0·150	33·3	3055	78·0	17·05	6·59	5·86	2400	1·08	710	Insp. 2·55 20·79

* In this and all later experiments *b*-samples in cols. 6 and 7.

VI. J. L. June 26, 1912, 2–4 p.m. CO_2 and oxygen in insp. air. Bar. 760, Temp. 19·5°, Load 2 kg.

1	2	3	4	5	6	7	8	9	10	11	
−132	0·690	7·2	1030	5·00	—	5·03	4·67	—	—		Insp. 0·05 20·66
−121	0·620	8·1	1094	5·95	—	5·76	5·24	—	—		Insp. 2·17[1]
−110	0·523	9·6	1462	9·80	—	6·15	5·47	—	—		Insp. 3·60
−26	0·747	6·7	969	4·27	—	5·60	5·20	—	—		Insp. 0·05[2] 90·85
−14	0·710	7·0	1036	4·87	—	6·04	5·49	—	—		Insp. 2·41[3]
−2·1	0·613	8·2	1335	7·51	—	6·63	5·90	—	—		Insp. 3·97
+0·20	0·049	20·4	2780	43·3	—	6·35	5·65	—	—	1150	
+0·47	0·051	19·6	2990	45·0	—	6·68	5·94	—	—	1063	Insp. 3·77
+0·77	0·044	22·7	2980	51·8	—	7·50	6·67	—	—	1052	
+1·9	0·393	25·5	3180	62·2	—	8·02	7·14	—	—	853	
+3·3	0·173	28·9	3025	67·0	—	7·95	7·07	—	—	866	Insp. 3·63

[1] CO_2 on 10 m. earlier. [2] O_2 on 4 m. earlier. [3] CO_2 on 9 m. earlier.

VII. J. L. June 27, 1912, 11 a.m. CO_2 and diminished O_2 in insp. air. Bar. 762, Temp. 19·0°, Load 2·0 kg.

1	2	3	4	5	6	7	8	9	10	11	
−23	0·700	7·1	807	3·59	—	5·52	5·13*		—		
											Insp. 0·03
−21	0·663	7·5	878	4·24	—	5·30	4·92		—		18·42
−1·1	0·606	8·2	1314	7·45	—	5·98	5·31		—		Insp. 3·27
											17·55
+0·25	0·052	19·3	2980	43·95	14·47	5·90	5·25	1240	0·75	1014	
+0·53	0·051	19·6	3300	50·0	13·97	6·30	5·60	1575	0·76	1014	
+0·86	0·139	21·6	3355	56·0	13·63	6·85	6·08	1975	0·83	950	Insp. 3·14
											17·73
+2·1	0·280	35·7	3000	82·0	14·72	6·28	5·58	1969	1·10	735	Insp. 2·93
+2·5	0·164	36·6	2625	72·7							17·66

* CO_2 in alv. exp. air before exp. 5·08 %.

VIII. F. N. Sept. 3, 1912, 11.50 a.m.—2.30 p.m. Bar. 760, Temp. 18·0°, Load 3·5 kg.

1	2	3	4	5	6	7	8	9	10	11	Pulse rate per min. 12	
−160	0·242	20·6	591	5·13	—	4·45*	—	266†	0·90	—	85	
	0·233	21·4	475		—	4·47*	—			—		
−2·5	0·435	18·4	723	7·37	—	4·73* 4·83*	—			—	78	Insp. 20·19
+0·20	0·141	21·3	2540	40·7	15·89	4·25	3·77	1455	1·06	2375	151	
+0·52	0·106	28·3	2600	55·3	14·07	6·06	5·38	2820	1·06	2355		Insp. 20·12
+0·79	0·116	25·8	3490	69·5	13·60	6·93	6·15	3760	1·14	2070	170	
+1·50	0·176	28·3	3190	69·3	14·55	6·83	6·06	3065	1·37	1605	166	

* Haldane-Priestley exp. sample. † Resp. exper.

IX. A. K. Sept. 18, 1912, 10 a.m. Bar. 760, Temp. 14·6°, Load 2·5 kg.

1	2	3	4	5	6	7	8	9	10	11	12
−5·0	0·336	14·9	708	5·79	—	4·37	—	—	—	—	79
−2·0	0·310	16·1	881	8·50	—	3·78	—	—	—	—	78
										1492	
+0·26	0·076	26·4	2250	43·8	16·32	3·35	—	—	—	1647	
+0·42	0·093	32·2	2080	49·2	—	3·60	—	—	—	1593	165
+0·63	0·053	56·6	1490	58·6	—	3·95	—	—	—	1770	

X. J. L. Sept. 20, 1912, 10 a.m. Bar. 771, Temp. 14·6°, Load 3·0 kg.

1	2	3	4	5	6	7	8	9	10	11	12
−9	0·75	6·7	810	3·38	12·77	5·52	5·12	—	—	--	
−7	0·56	7·1	825	3·72	12·48	5·66	5·25	—	—	—	68·5
+0·19	0·084	23·8	2840	52·2	15·70	4·26	3·79	—	—	1881	
											151
+0·40	0·086	23·3	3060	55·2	15·83	4·69	4·17	—	—	1683	
											168
+0·69	0·113	26·5	3245	67·4	15·68	5·54	4·92	—	—	1470	
+0·85										1290	

XI. J. L. Aug. 27, 1912, 11 a.m. CO_2 in insp. air. Experiment on excitability of resp. centre. Bar. 740, Temp. 18·0°. Load 1·0 kg.

1	2	3	4	5	6	7	8	9	10	11	12	
−14	0·62	6·5	887	3·55	—	5·74	5·32	–	—	—	67·6	Insp. 0·00 CO_2
−12	0·81	6·2	891	3·43	—	5·76	5·35	—	—	—		
−2	0·75	8·0	1201	6·27	13·59	6·40	5·82	—	—	—	70·4	Insp. 3·20 CO_2
−1	0·565	7·1	1261	5·91	—	6·47	5·88	—	—	—		
+6	0·395	12·6	2290	21·0	14·20	6·40	5·22	—	—	379	100·1	Insp. 0·23 CO_2
+7	0·330	12·1	2180	19·0	—	6·45	5·27	—	—	365		
+15	0·336	14·9	2590	26·3	13·26	7·20	5·88	1110	—	367	100·0	Insp. 2·94 CO_2 18·13 O_2
+16	0·328	15·2	2715	30·5	—	7·20	5·88	—	—	367		Insp. 2·94 CO_2
+23	0·316	12·6	1883	16·9	13·01	6·68	5·45	1025	—		100·0	Insp. 0·28 CO_2
+24	0·334	12·0	1930	16·15	—	6·60	5·39	—	—	367		20·26 O_2